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(54) Title: ANTICOAGULANT COMPOSITION

(57) Abstract: A solid heparin tablet composition has a melting point of 25 °C or higher and comprises a continuous lipid component comprising one or more polar lipids, one or more non-polar lipids, optionally one or several of water and mono- to trivalent alcohol in an amount of up to 15% by weight of the composition, and heparin selected from native heparin and fractionated heparin. Also disclosed is a corresponding tablet, processes for production of the composition and the tablet, and a method of preventing or treating conditions amenable to preventive or therapeutic treatment by administration of the tablet.

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ANTICOAGULANT COMPOSITION

FIELD OF THE INVENTION

The present invention relates to an oral heparin tablet composition, a corresponding tablet, and to corresponding methods of manufacture.

BACKGROUND OF THE INVENTION

Heparin, whether normal (native, not fractionated) or partially degraded (fractionated), is an important anticoagulant. It is administered to persons with increased risk for blood clot formation, such as persons having undergone surgery or severe trauma or whose blood coagulation system is not well balanced, such in persons with risk for deep venous thrombosis. The drawback with this cheap and efficient drug is the requirement of administration by injection.

OBJECTS OF THE INVENTION

It is an object of the invention to provide an oral heparin tablet composition that exploits the advantageous properties of lipids as pharmaceutical carriers in regard of gastroinstestinal uptake and/or sustained release and/or convenience and/or economy.

It is another object of the invention to provide a corresponding carrier composition for incorporation of heparin.

It is a further object of the invention to provide processes for making the aforementioned carrier composition and for incorporating heparin into said carrier composition.

Further objects of the invention will be evident from the following short description of the invention, the

description of preferred embodiments, and the appended claims.

SHORT DESCRIPTION OF THE INVENTION

According to the present invention is disclosed a solid heparin composition for oral administration which has a melting point of from 25°C to 50°C or more, preferably from 30°C to 45°C, more preferred from 33°C to 42°C, comprising a continuous lipid phase comprising, preferably consisting of, a polar lipid component, a non-polar lipid component, and a pharmacologically efficient amount of heparin which may be native (non-degraded) or degraded (fractionated) heparin. The polar lipid component consists of one or more polar lipids. The non-polar component consists of one or more non-polar lipids. The one or more polar lipids are membrane lipids, in particular glycolipids and phospholipids. The one or more non-polar lipids are preferably glycerides, i.e. glycerol esters of fatty acids (mono-, di-, and triglycerides). All polar and non-polar lipids of the invention can be sourced from foodstuffs or food grade material. The polar lipids of the invention are amphiphilic with headgroups such as galactose or phosphate esters. The polar lipid component of the invention is combined with the non-polar lipid component in various proportions to allow the controlled incorporation of pharmaceutical including food supplement agents. It is believed that the incorporation mechanism is based on interactions of the polar headgroups and the lipophilic chains of the non-polar component with the compound to be incorporated. Pharmacologically efficient compositions for heparin, optionally in admixture with other pharmacologically active agents, can be experimentally determined by varying the ratio of the polar to non-polar component. To a certain extent the pharmacological efficacy of the composition is

also influenced by the composition of the polar and non-polar component, respectively.

Preferably the polar component of the solid heparin composition according to the invention comprises or, more preferred, consists of one or several polar lipids of vegetable origin, such as oat kernels or soybeans. Preferably the non-polar lipid component of the composition according to the invention comprises or, more preferred, consists of one or several glycerides of vegetable origin, such as palmkernel oil, coconut oil, palm oil and cottonseed oil.

It is particularly preferred for the solid heparin composition of the invention to comprise lipid material of vegetable origin only.

According to the present invention is also disclosed a solid heparin oral tablet produced from the aforementioned pharmaceutical or food supplement composition, in particular by compression moulding or casting.

In the pharmaceutical literature lipid continuous phases are described as oily liquids, which need to be administered as oral liquids or enclosed in hard or soft shell capsules. However, such oily liquids are completely outside of the scope of the present invention. Lipid phases are also known in form of dispersions, i.e. dispersed aqueous solvents. Lipid emulsions and liposome preparations are examples of such dispersions which, by definition, are not lipid continuous phases and therefore do not form part of the present invention.

The polar component of the invention can be described as formed of membrane lipid(s), i.e. the lipid constituents of biological membranes. Membrane lipids contain a polar, hydrophilic, head group and one or more lipophilic hydrocarbon chains. This combination makes the membrane lipid molecules amphipathic and enables them to associate both with water and oils. Such membrane lipids can be classified according to their chemical structure, which is a function of

how the polar head group is linked to the lipophilic chains. Sphingolipids (linked by sphingosine) and glycerolipids (linked by glycerol) are the two main groups. Depending on the characteristics of the polar head group sphingolipids and glycerolipids can be further classified as phospholipids, with the head group being a phosphate ester, or as glycolipids, with the head group being a carbohydrate. Depending of the specific nature of the carbohydrate group membrane lipids sometimes are called, for example, galactolipids, which are glycerolipids with galactose in the polar head group. Examples of common membrane lipids are phosphatidylcholine (PC), phosphatidylethanolamine (PE), and digalactosyldiacylglycerol (DGDG). The membrane lipids can be extracted from, for example, egg yolk (egg lecithin), milk and dairy products, soybeans (soy lecithin), other oil crops, oat kernels, and other cereals and grains. These extracts can be further treated to become, for example, PC from soybeans and galactolipids from oats. Preferred polar lipids are galactolipids from oat kernels (CPL-galactolipid) or from soybeans (soy lecithin or soy-PC).

Synthetic polar lipids and membrane lipid analogues based on a carbohydrate or phosphate ester moiety are comprised by the polar lipid component of the invention.

The preferred non-polar lipids of the invention are fatty acid esters of glycerol. These esters include mono-, di-, and triglycerides. Edible oils are triglyceride oils, from which mono- and diglycerides can be derived. Other non-polar lipids of the invention include vegetable and animal oils from various sources, synthetic oils, fatty acids, natural and synthetic glycerides, sterol esters, fatty alcohols. Synthetic non-polar lipids and fatty acid analogues are also comprised by the invention. A description of the area of polar and non-polar lipids is given in "Fatty Acid and Lipid Chemistry" (Frank Gunstone, 1996, Blackie Academic & Professional, Chapman & Hall).

The triglyceride may be selected from palmkernel oil or natural oils with similarly, relatively high solid fat content or melting range. Preferred non-polar lipids include palmkernel oil fractions, obtained by commercial fractionation of palmkernel oil into specific mixtures of triglycerides, e.g. palmkernel stearin, based on the combination of mainly lauric, myristic, and palmitic esters of glycerol. Preferred monoglycerides are selected from edible oil derived monoglycerides, in particular medium chain monoglycerides (chain length C_8 - C_{10}), derived from coconut oil, and normal chain monoglycerides (chain length C_{16} - C_{18}), derived from most vegetable oils.

According to a preferred aspect of the invention the continuous lipid phase may comprise up to 15% by weight, preferably up to 10% by weight, most preferred up to 5% by weight of water and/or an alcohol, including a alkanediol or -triol, such as ethanol, 1,2-propylene glycol, low molecular weight polyethylene glycol, and glycerol. By definition the continuous lipid phase cannot comprise more water or alcohol than is compatible with its property of being continuous.

According to the invention is also disclosed a carrier composition for heparin consisting of a continuous lipid phase having a melting point of from 25°C to 50°C or more, preferably from 30°C to 45°C, more preferred from 33°C to 42°C, comprising, preferably essentially consisting of, a polar lipid component in combination with a non-polar lipid component.

According to the present invention is furthermore disclosed a process for the production of a heparin tablet composition which has a melting point of from 25°C to 50°C or more, preferably from 30°C to 45°C, more preferred from 33°C to 42°C, comprising a continuous lipid phase comprising, preferably consisting of, a polar lipid component, a non-polar lipid component and native (essentially non-degraded) or fractionated (degraded) heparin, comprising mixing a polar

lipid component with a non-polar lipid component at a first temperature at which at lease one of said components is in a liquid state, thereby obtaining a liquid continuous lipid phase, dissolving a pharmacologically effective amount of heparin in the liquid continuous lipid phase, cooling the solution thus obtained or aliquots thereof to a second temperature at which it solidifies, said second temperature ranging from 25°C to 50°C or more, preferably from 30°C to 45°C, more preferred from 33°C to 42°C. The cooling may produce a cake if carried out in bulk or a powder if the liquid product is fed to a nozzle, preferably at a temperature slightly above its melting point, and sprayed on, for instance, a cooled metal surface, in particular a polished chromium plated stainless steel surface in form of a band running on rollers. A powderous product may also be obtained by spraying the liquid product into a atmosphere of a temperature below the solidification temperature of the liquid product. The cake may be transformed into powder by, for instance, grinding at a low temperature.

According to a second preferred aspect is disclosed a heparin tablet of the invention coated with one or several layers of tablet coating excipients, such as to provide the tablet with an enteric coat and/or a coat physically stabilizing the tablet at a temperature at or above its melting point, and a corresponding coating process. Particularly preferred is a tablet of the invention provided with a first or only coat applied by a dry coating process comprising mechanically working a coating powder into the surface of the tablet at a temperature at which the tablet is sufficiently soft for the powder particles to adhere and allow them being worked into its surface but not sufficiently soft for substantial deformation, in particular at a temperature from 25°C to 10°C below the melting point of the tablet. One or more additional layers may be added to the thus coated tablet by routine pharmaceutical coating

processes known in the art. The tablet of the invention may also be built up around an inert nucleus.

A tablet according to the invention can be produced from the heparin oral tablet composition of the invention by compressing the aforementioned powderous product or by moulding or any other suitable process. According to a preferred aspect of the invention the moulding is carried out in a mould covered with an anti-adhering agent or layered

By way of examples it was surprisingly found that the solid heparin oral tablet composition of the invention increases the uptake of heparin in the gastrointestinal tract and/or prolongs its efficacy.

In the following the invention will be explained in more detail by the following, non-limiting examples.

DESCRIPTION OF PREFERRED EMBODIMENTS

Materials. The lipid materials used are listed in Table 1.

Table 1. Lipid materials

Trade name and source
Galactolipids from oats (CPL-Galactolipid; Lipid Technologies Provider AB, Karlshamn, Sweden)
Medium chain monoglyceride (Akoline MCM; Karlshamns AB, Karlshamn Sweden)
Palmkernel stearin (fraction of palmkernel oil ; Karlshamns AB, Karlshamn Sweden)
Heparin (low molecular weight; Calbiochem, p.no. 375097
Hydrogenated cotton seed oil (Akofine NF; Karlshamns AB, Karlshamn Sweden)

EXAMPLE 1. Preparation of a tablet by casting molten lipid mixture into a mould.

Tablet ingredients (in g) are shown in Table 2.

Table 2. Tablet composition

Tablet preparation	*A*	*B*	*C*	*D*
Heparin*	0.08	0.18	0.21	0.0
Water	0.40	0.90	0.70	0.70
Monoglyceride	0.92	0.90	0.72	0.70
CPL-Galactolipid	1.24	2.79	2.17	2.17
Palmkernel stearin	1.40	3.15	2.31	2.52

*Low Molecular Weight Heparin (LMWH)

The ingredients were blended and the mixture melted by heating to a temperature of 60 C and stirred at this temperature for 5 hours when all heparin had dissolved. Aliquots (0.24 g) of the melted phase were cast in a mould covered with hydrogenated triglyceride (Akofine NF™) powder. The mould was cooled in a freezer and the tablets recovered.

EXAMPLE 2. Animal study.

NZW rabbits were used in all experiments and tablets were administered orally. The animals were given four or six tablets followed by water until they had swallowed the tablets. The animals were deprived of food for about 18 hours before dosing. Blood samples were drawn from the ear veins in sodium citrate vials before dosing and ½, 1, 4, 6, and 8 hours after dosing for determination of APTT (Activated Partial Thromboplastin Time) on an IL Coagulation Systems ACL 2000 apparatus. The blood samples were centrifuged for 10 minutes at approximately 1270 G to obtain plasma for the analysis.

The results expressed as % change from baseline were individually calculated for each animal. The APTT value in the blood sample taken prior to dosing is regarded as baseline for each animal. The results are shown in Table 3.

Table 3. APTT measurements in rabbits

Tablet Preparation (LMWH IU/kg)	Time after dosing (hours)							No. of animals
	0	0,5	1	2	4	6	8	
A - 475	0	47	51	63	-5	35	8	3
B - 700	0	-9	51	23	35	26	-14	4
C - 1000	0	30	39.5	47	42.5	57	52.3	3
D - 0	0	-15	4	6	-22	-9	-5	7

Claims

1. A solid oral heparin tablet composition which has a melting point of 25°C or higher, comprising a continuous lipid component comprising one or more polar lipids, one or more non-polar lipids, optionally one or several of water and mono- to trivalent alcohol in an amount of up to 15% by weight of the composition, and heparin selected from native heparin and fractioned heparin.

2. The composition of claim 1, substantially consisting of one or more polar lipids, one or more non-polar lipids, and heparin.

3. The composition of claim 1, substantially consisting of one or more polar lipids, one or more non-polar lipids, water up to 15% by weight, and heparin.

4. The composition of claim any of claims 1-3, wherein said one or more polar lipids are membrane lipids.

5. The composition of claim 4, wherein said one or more polar lipids are selected from glycolipids.

6. The composition of any of claims 1-5, wherein said one or more non-polar lipids are glyceride esters of fatty acids.

7. The composition of any of claims 1-6, wherein said one or more non-polar lipids are lipids of vegetable origin.

8. The composition of claim 7, wherein said one or more non-polar lipids include triglycerides selected from palmkernel oil fractions obtained by commercial fractionation of palmkernel oil.

9. The composition of claim 7, wherein said one or more non-polar lipids include C_8 - C_{10} monoglycerides and/or C_{16} - C_{18} monoglycerides.

10. The composition of claim 1, comprising water and one or more of mono- to trivalent alcohol.

11. The composition of claim 10, wherein the monovalent alcohol is ethanol.

12. The composition of claim 11, wherein the divalent to trivalent alcohol is selected from 1,2-propylene glycol, low molecular weight polyethylene glycol, glycerol. The composition of any of claims 1 and 3-13, comprising up to 10% by weight of water.

13. The composition of claim 12, comprising up to 5% by weight of water.

14. The composition of claim 4, wherein said one or more polar lipids are selected from phospholipids.

15. A process for the production of an oral heparin tablet which has a melting point of from 25°C and higher, comprising:

- mixing one or several polar lipids with one or several non-polar lipids at a first temperature at which at least one of said components is in a liquid state,
- dissolving, in the liquid continuous lipid phase obtained, heparin selected from native heparin and fractionated heparin,
- cooling the solution of heparin in the lipid phase or portions thereof to a second temperature at which it solidifies,
- forming tablets by carrying out the cooling step with aliquots of the solution or from a bulk product obtained in the cooling step.

16. The process of claim 17, wherein said first temperature is 25°C and higher.

17. The process of claim 15 or 16, wherein said solution is cooled in bulk, comprising forming a powderous product from said bulk product.

18. The process of claim 15 or 16, wherein said solution is fed to a nozzle and sprayed on a surface or into a cavity having a temperature below the melting point of the liquid, thereby forming a powderous product.

19. A process for the production of an oral heparin tablet comprising compressing the powderous product of claim 17 or 18 into a tablet.

20. The process of claim 19, comprising covering the punch(es) and/or the die for pressing the tablet with an anti-adherent prior to compression.

21. The process of claim 20, wherein the anti-adherent is selected from stearic acid or a salt thereof.

22. The process of claim 15, wherein the cooling is carried out by pouring an aliquot of said solution into a mould, thereby forming a tablet.

23. The process of claim 22, wherein the mould is covered with an anti-adherent prior to pouring.

24. The process of claim 23, comprising coating said tablet with one or several powderous pharmaceutical excipients.

25. The process of claim 24, wherein said one or several excipients are mechanically worked into the surface of the tablet so as to form a coating.

26. An oral heparin tablet essentially consisting of a continuous lipid phase, optionally comprising an inert nucleus, wherein the lipid phase may optionally comprise one or several of water and mono- to trivalent alcohol in an amount of up to 15% by weight of the lipid phase, the composition having a melting point of 25°C or higher and comprising one or more polar lipid components in combination with one or more non-polar lipid components, and heparin selected from native heparin and fractionated heparin.

27. An oral heparin tablet comprising a core which has a melting point of 25°C or higher, the core consisting of

a continuous lipid phase and optionally comprising an inert nucleus, the continuous lipid phase comprising one or several polar lipid components, one or several non-polar lipid components, wherein the lipid phase may optionally comprise one or several of water and mono- to trivalent alcohol in an amount of up to 15% by weight of the lipid phase, and heparin selected from native heparin and fractionated heparin, further comprising a coat consisting of pharmaceutical excipients.

28. The tablet of claim 26 or 27, wherein the coat comprises one or more subcoats consisting of pharmaceutical excipients.

29. A method of treating or preventing a condition amenable to treatment or prevention by administration of a pharmacologically effective dose of heparin, characterized in that the heparin is administered in form of the tablet of claim 26-28.

30. The method of claim 29, wherein said condition is one of deep venous thrombosis, blood clots, pulmonary embolism, unstable angina, atrial fibrillation, acute myocardial infarction, coronary angioplasty, stent placement, coronary artery bypass graft, pulmonary embolism, stroke.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 03/00973

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/727, A61K 47/44, A61K 9/20
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI DATA, EPO-INTERNAL, CA DATA, EMBASE, MEDLINE, BIOSIS, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	European Journal of Pharmaceutical Sciences, Volume 1, 1994, L. Lohikangas et al: "Relative contribution of phosphatidylcholine and monoglyceride to absorption enhancement of low molecular weight heparin (Fragmin) by a new lipid-based drug delivery system in monolayers of human intestinal epithelial Caco-2 cells and after rectal administration to rabbits", page 307 - page 312, abstract, 3.1, 3.3, discussion --	1-30
X	WO 0191729 A1 (BASF AKTIENGESELLSCHAFT), 6 December 2001 (06.12.01), example 5 --	1-30
X	WO 9319737 A1 (KABI PHARMACIA AB), 14 October 1993 (14.10.93), example 1 --	1-30

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 Sept 2003	29-09-2003
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Ingrid Eklund/EÖ Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5626869 A (HÅKAN NYQVIST ET AL), 6 May 1997 (06.05.97), examples 6-7	1-30
A	US 5082667 A (KURT G. VAN SCOIK), 21 January 1992 (21.01.92), example 2	1-30
A	WO 9205771 A1 (KABI PHARMACIA AB), 16 April 1992 (16.04.92), page 23, claim 18	1-30
A	EP 0368247 A2 (TAKEDA CHEMICAL INDUSTRIES, LTD.), 16 May 1990 (16.05.90), examples 1-2	1-30
E,X	WO 03049721 A1 (COSMO S.P.A.), 19 June 2003 (19.06.03), examples 1-14, claims 1-3	1-30
E,X	WO 0247663 A1 (F. HOFFMAN-LA ROCHE AG), 20 June 2002 (20.06.02), claims 1-8	1-30

INTERNATIONAL SEARCH REPORT

International application No.
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Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 29-30
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE03/00973

Claims 29-30 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNAT[redacted]AL SEARCH REPORT

Information on patent family members

26/07/03

I[redacted]ational application No.
PCT/SE 03/00973

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INTERNATIONAL SEARCH REPORT

Information on patent family members

26/07/03

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